UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: October 29, 2013

TXR #: 0056794

SUBJECT: **Endothall:** Summary of Hazard and Science Policy Council (HASPOC) Meetings: Recommendations on the need for an immunotoxicity study.

PC Code: 038904
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0056794
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: N/A
40 CFR: N/A

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THROUGH: Jess Rowland, Co-Chair
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HASPOC
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TO: John Liccione, Toxicologist
Michael Metzger, Branch Chief
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MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jeff Dawson, Jeff Evans, Jess Rowland, John Kough, Jonathan Chen, Mike Metzger

Presenter: John Liccione

Other Attendees: Christopher Schlosser, Donna Davis, Ivan Nieves, Jaime D'Agostino, Jonathan Leshin, Julie Van Alstine, Kelly Lowe, Kristin Rury, Lata Venkateshwara, Matt Lloyd, Monique Perron, Ronnie Bever, Thurston Morton, Uma Habiba

I. PURPOSE OF MEETINGS

The Hazard and Science Policy Council (HASPOC) met on September 26, 2013 to discuss the Registrant's waiver request (MRID 49177602) for the immunotoxicity study on endothall, a dicarboxylic acid that is a selective contact herbicide, defoliant, desiccant, growth regulator, and aquatic algaecide, and to determine the need for an immunotoxicity study to support the registered uses of endothall.

II. SUMMARY OF USE & TOXICOLOGY PROFILES AND RISK ASSESSMENT

a. Use Profile

Endothall [7-oxabicyclo[2,2,1] heptane-2,3-dicarboxylic acid] is a selective contact herbicide, defoliant, desiccant, and aquatic algicide which belongs to the dicarboxylic acid chemical class. Endothall (PC Code 038901) and its dipotassium (PC Code 038904) and alkylamine (PC Code 038905) salts are registered primarily as aquatic herbicides to control a variety of plants including plankton, pondweed, naiad, coontail, milfoil, elodea, and algae in water bodies. They are also registered for desiccation/defoliation of alfalfa/clover (grown for seed only), cotton, and potatoes prior to harvest, and for reduction of sucker branch growth in hops.

Endothall acid and its dipotassium and mono-N, N-dimethylalkylamine salts are FIFRA List B chemicals. Although there are other inactive Endothall salts in Case 2245, only the active compounds, endothall acid (PC 038901) and its dipotassium (PC 038904) and mono-N, N-dimethylalkylamine (PC 038905) salts are being considered in this reregistration.

The endothall formulation classes which are registered on food/feed crops include the granular (G) and soluble concentrate liquid (SC/L). The G formulations typically contain 10.1%, 11.2%, or 63% acid equivalent (ae), and the SC/L formulations contain 0.52, 2.0, or 3.0 lb ai/gal. Both formulation classes may be applied using waterborne, ground or aerial equipment. The maximum treatment rate of endothall, when applied on aquatic areas (including irrigation and drainage canals, lakes, and ponds where water may be used as potable water) is 5 ppm. When applied on agricultural crops, the maximum registered seasonal rates range from 0.10 to 2.0 lb ae/A with preharvest intervals of 3 to 85 days.

Endothall is applied as a spray with aerial and ground boom equipment when used as a harvest-aid agent and when used as a sucker suppressant on hops, endothall is applied with ground equipment only. When used as an aquatic herbicide, a variety of equipment may be used. Boats used to treat aquatic weeds are normally designed to apply sprays and granular applications from the bow. For occupational applications of liquid formulations to water, endothall may be sprayed onto the water surface using hand-held or boat-mounted equipment similar to handgun sprayers (for smaller-scale applications). Endothall may also be directly metered into the suction side of a pump and injected below the surface of the water. This technique is the only method of application to flowing waters, but is also used for applications to quiescent waters. For occupational applications of granular formulations to water, ground boom data from PHED data base is used. For Residential applications of granular formulations to water, HED assumes that a belly-grinder-type granular spreader is use

b. Toxicity Profile

Endothall is a caustic chemical with toxicity being the result of a direct degenerative effect on tissue. Dermally, it destroys the stratum corneum and then the underlying viable epidermis. Orally, it attacks the digestive tract. The dog is particularly sensitive to endothall toxicity. Orally, it attacks the canine digestive tract at relatively low doses and then the liver and kidneys at lethal doses. The rabbit is extremely sensitive to ocular instillation of endothall. In the eye irritation study, endothall technical was extremely irritating to the eye, and was also lethal to 4/6 rabbits tested. In a dermal irritation study, endothall was an extreme irritant (category I). Although it was classified as a category III in an acute dermal toxicity study, endothall has been shown to be a severe irritant in a dermal absorption study (MRID 42169503) and in a 21-day dermal toxicity study (MRID 43465201) after one application. Based on all available data, endothall is classified as a severe dermal irritant. Endothall is also an extreme irritant by the acute oral and acute ocular routes of administration (category I), and is a skin sensitizer. In the acute inhalation study, it was classified as (category III however, there was irritation and other respiratory effects observed in 5-day and 28-day inhalation toxicity studies supporting the conclusion of the irritant effects of endothall.

The most sensitive effect of endothall following oral administration is direct irritation of the gastrointestinal system. This effect was evident in several species and in several studies. Proliferative lesions of the gastric epithelium were observed in F_1 parental male and female rats treated orally with 2 mg/kg/day endothall in a 2-generation reproduction study (a NOAEL was not identified). Endothall caused gastric epithelial hyperplasia in dogs treated with an oral dose of 6.5 mg/kg/day for 52 weeks (a NOAEL was not determined).

Besides gastric irritant effects, decreased body weight was also a sensitive effect following endothall administration. The decreased body weights were most likely attributable to the constant and direct irritation of the gastric lining. In a developmental rat study, pregnant rats exhibited decreased body weight following oral treatment with 25 mg/kg/day endothall; the NOAEL was 12.5 mg/kg/day. Decreased body weight was noted in a 90-day dietary study in the rat (LOAEL = 118 mg/kg/day; NOAEL = 39 mg/kg/day). Body weight loss occurred in dogs following a 13 week oral treatment with endothall (LOAEL = 27.5 mg/kg/day; NOAEL = 11.7 mg/kg/day). A LOAEL of 45 mg/kg/day for body weight decrement was identified in an oral carcinogenicity mouse study.

HED selected the following toxicity endpoints (and points of departure) which are the same that were used in the previous 2005 risk assessment with the exception of those for inhalation exposure. For the inhalation exposure scenarios, the recently submitted inhalation toxicity study was identified as the most appropriate study.

Acute Dietary: An acute dietary hazard value was not identified for the general population or for females of child-bearing age (13-49 years old). This is because there is no appropriate endpoint attributable to a single dose in any of the studies submitted.

Chronic Dietary: For chronic dietary exposure, the toxicology endpoint was selected from a 2-generation reproduction toxicity study in rats in which the LOAEL was 2 mg/kg/day based on proliferative lesions of the gastric epithelium in both sexes. The Uncertainty Factor includes the 10x for interspecies extrapolation and 10x for intraspecies variation, and an additional 3x FQPA

factor for the lack of a NOAEL in the study used for endpoint selection. A 3X FQPA factor (as opposed to a 10X) was determined to be adequate since the severity of the lesions were minimal to mild.

Dermal: Since endothall is so toxic at the portal of entry (e.g., skin), quantification of systemic toxicity and risk resulting from dermal exposure will not be done, and a dermal absorption factor will not be estimated. In the 21-day dermal toxicity study (MRID 4346520), severe dermal effects were observed at 30 mg/kg/day (the lowest dose tested). The NOAEL for dermal irritation was not established due to erythema, edema, and fissuring and sloughing off of the skin at the dose site at the lowest dose tested (30 mg/kg/day). Endothall is caustic dermally because it is an acid, and mitigation of any potential dermal effects can be addressed with precautionary labeling recommending the use of gloves and other personal protection which limits contact of the material with the handler's body.

Inhalation: Residential handler exposure is expected to be short-term in duration. For this short-term inhalation exposure scenario, a NOAEL of 0.001 mg/L was selected from a 28-day inhalation toxicity study in the rat based on clinical signs of toxicity observed acutely at 0.005 mg/L. These signs, indicative of pulmonary toxicity, included rales and labored breathing and were seen daily (0-1 hr post dosing, prior to next exposure, and in detailed examinations). Although the 5-day inhalation study also revealed acute signs of pulmonary toxicity, a NOAEL was not identified, but the results of the study support the findings of the 28-day inhalation study. Therefore, the NOAEL for acute signs noted in the subchronic inhalation study was selected for the short-term residential exposure scenario. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

For the short- and intermediate- term occupational inhalation risk assessment, a NOAEL = 0.001 mg/L was selected from a 28-day inhalation toxicity study in the rat in which the LOAEL was 0.005 mg/L based on indications of lung toxicity (rales in males and increased lung weights and alveolar macrophages in both sexes). Long-term inhalation exposures are not anticipated.

Incidental Oral: The short-term incidental oral risk assessment for endothall is based on a NOAEL of 9.4 mg/kg/day based on decreased pup body weight (both sexes) on Day 0 of the $F_1$and F_2 generations in a 2-generation rat reproduction (oral feeding) study. This endpoint is appropriate with respect to the duration and population of concern (i.e., swimmers incidental oral ingestion in adult and children).

Intermediate- and long-term incidental oral exposures are not expected.

c. Evidence of Immunotoxicity in the Endothall Database of Toxicology Studies

There are no signs of immunotoxicity following subchronic or chronic dosing in multiple species in the endothall database.

Parameters	Findings
Hematology Indicators (WBC changes)	None

Clinical Chemistry Indicators (A/G Ratio)	None
Organ Weight Indicators (Spleen, Thymus)	None
Histopathology Indicators (Spleen, Thymus, Lymph nodes)	None
Toxicity Profile (Target Organs)	Stomach (oral) Lung (inhalation)

d. Evidence of Immunotoxicity in the Database for Other Carboxylic Pesticides (SAR Analysis)

Endothall [7-oxabicyclo[2,2,1] heptane-2,3-dicarboxylic acid] is a selective contact herbicide, defoliant, desiccant, and aquatic algicide which belongs to the dicarboxylic acid chemical class. Other carboxylic acid pesticides include aminocyclopyrachlor, aminopyralid, and clopyralid. Immunotoxicity studies have been performed on aminocyclopyrachlor (both rat and mice) and clopyralid but not aminopyralid. The available studies did not indicate an immunotoxic potential.

Aminocyclopyrachlor	
MRID No.	**47560025 (Rat Study)**
Immunotoxicity NOAEL	1277 mg/kg/day (HDT)
Immunotoxicity LOAEL	Not established
Basis for LOAEL	None
Systemic toxicity NOAEL	1277 mg/kg/day
Systemic Toxicity LOAEL	Not established
Basis for the LOAEL	None
MRID No.	**47560026 (Mouse Study)**
Immunotoxicity NOAEL	1056 mg/kg/day (HDT)
Immunotoxicity LOAEL	Not established
Basis for LOAEL	None
Systemic toxicity NOAEL	1056 mg/kg/day
Systemic Toxicity LOAEL	Not established
Basis for the LOAEL	None

Clopyralid	
MRID No.	48300001
Immunotoxicity NOAEL	1062 mg/kg/day (HDT)
Immunotoxicity LOAEL	Not established
Basis for LOAEL	None
Systemic toxicity NOAEL	1062 mg/kg/day (HDT)
Systemic Toxicity LOAEL	Not Established
Basis for the LOAEL	None

III. STUDY WAIVER REQUESTS:

A waiver is requested for an immunotoxicity study (MRID 49177602) , based on the following considerations:

- The toxicology database for endothall does not reveal any evidence of treatment-related effects on the immune system suggesting that immune system is not the primary target organ.
- The known target organs of endothall are the stomach (oral exposure) and the lungs (inhalation exposure).
- The most sensitive endpoints currently used to assess exposure and risk is considered protective of any potential immunotoxicity.
- There was no evidence of immunotoxicity for two structurally related pesticides (aminocyclopyrachlor and aminopyralid) at the highest dose tested in guideline Immunotoxicity studies.
- Immunotoxicity did not impact the PODs and toxicity endpoints of concern used for human health risk assessments for these pesticides.

IV. HASPOC RECOMMENDATION

Therefore, based on a WOE approach, the HASPOC recommends that an immunotoxicity study is not required for endothall. The target organs are the stomach and the lung and the database did not reveal any evidence for immunotoxicity An immunotoxicity study is not anticipated to provide a lower POD or result in a more sensitive endpoint than those already used for the endothall risk assessment.